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Exposure of nonsmoking women to environmental tobacco smoke: a 10-country collaborative study

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The interpretation and interpretability of epidemiologic studies of environmental tobacco smoke (ETS) depend largely on the validity of self-reported exposure. To investigate to what extent questionnaires can indicate exposure levels to ETS, an international study was conducted in 13 centers located in 10 countries, and 1,369 nonsmoking women were interviewed. The present paper describes the results of the analysis of self-reported recent exposure to ETS from any source in relation to urinary concentrations of cotinine. Of the total, 19.7 percent of the subjects had nondetectable cotinine levels, the median value was 6 ng/mg, and the cut-point of the highest decile was 24 ng/mg. The proportion of subjects misreporting their active smoking habit was estimated at between 1.9 and 3.4 percent, depending on whether cut-points of 50 or 100 ng/mg creatinine were used. Large and statistically significant differences were observed between centers, with the lowest values in Honolulu, Shanghai, and Chandigarh, and the highest in Trieste, Los Angeles, and Athens. Mean cotinine/creatinine levels showed a clear linear increase from the group of women not exposed either at home or at work, to the group of those exposed both at home and at work. Values were significantly higher for women exposed to ETS from the husband but not at work, than for those exposed at work but not from the husband. The results of linear regression analysis indicated that duration of exposure and number of cigarettes to which the subject reported being exposed were strongly related to urinary cotinine. ETS exposure from the husband was best measured by the number of cigarettes, while exposure at work was more strongly related to duration of exposure. After adjustment of number of cigarettes for volume of indoor places, a similar increase in cotinine (5 ng/mg) was predicted by the exposure to 7.2 cigarettes/8 h/40 m^3 from the husband and 17.9 cigarettes/8 h/40 m^3 at work. The results indicate that, when appropriately questioned, nonsmoking women can provide a reasonably accurate description of ETS exposure. Assessment of individual exposure to ETS should focus on daily duration and volume of *indoor* places where exposure occurred.

Key words: Home exposure, international study, passive smoking, self-reported exposure, urinary cotinine, work exposure.

Introduction

The number of investigations on the health effects of environmental tobacco smoke (ETS) has grown substantially in recent years following initial reports of an association of ETS with lung cancer risk in nonsmokers.[1,2] Two comprehensive reviews on measuring exposures to ETS and assessing the associated health risks appeared in 1986.[3,4] They conclude, as does the IARC Monograph on Tobacco Smoking,[5] that a causal relationship

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between exposure to ETS and lung cancer is supported by epidemiologic evidence and is biologically plausible.

A difficulty in interpreting the results of studies on ETS and lung cancer stems from the way exposure was determined in most studies, namely by: (i) focusing on the smoking habits of the spouse with little consideration of other sources of ETS; (ii) limiting the assessment to a qualitative evaluation of 'exposed' or 'not exposed' rather than a quantitative scale of total exposure to ETS. In the absence of objective measurements, this can pave the way to a variety of misreporting errors which can substantially bias study results, especially if the likely effect of ETS is small.[6] Therefore, a method of validating exposure to ETS by biochemical measures has become increasingly important.[7]

To investigate to what extent questionnaires can indicate exposure levels to ETS, we have conducted an international study in a variety of local settings (13 centers in 10 countries) with two main objectives: (i) to validate self-reported recent exposure to ETS from any source against the urinary concentrations of an exposure-specific marker (cotinine); and (ii) to compare urinary levels of cotinine and patterns of ETS exposure among nonsmoking women in different countries. The present report is focused particularly on the first objective.

Subjects and methods

Thirteen centers located in Canada (Toronto), People's Republic of China (Shanghai), Greece (Athens), Federal Republic of Germany (Bremen), Hong Kong, India (Chandigarh), Italy (Turin and Trieste), Japan (Sendai/Miyagi), Poland (Warsaw), and the US (Los Angeles, New Orleans, and Honolulu) took part in the study. Study subjects were women who were known to be nonsmokers. In some centers they were control subjects of previous or ongoing case-control studies, while in other centers they were volunteers from stratified population samples. If numbers permitted, 50 percent of these women were to be currently married to a smoker and the other 50 percent currently married to a nonsmoker (or unmarried); within each of these categories 50 percent were to be women currently employed. Four sampling groups were thus formed.

Data collection at the participating centers started in February 1986 and was completed by June 1986. Urinary chemical determinations were completed within six months of receipt of samples.

The interview

Each subject was interviewed by a nonsmoking interviewer (one to three interviewers were used at each center) at a convenient time of day. At most centers the interview took place at home, but at three centers (Trieste and, for some subjects, Chandigarh and Sendai) interviews took place in the waiting room of out-patient departments or other public institutions. Each woman was asked whether she had used any tobacco product in the past seven days. If the response was negative, the interviewer used, according to the instruction manual, a structured questionnaire which included detailed questions on:

- husband's smoking habits (general questions);
- husband's smoking in the home in the past seven days (detailed history for each occasion during which the woman was exposed over the last four days, and less detailed for the previous four);
- exposure to other people smoking at home (same detail as above);
- exposure to tobacco smoke at work (same detail as above);
- exposure to tobacco smoke in vehicles (same detail as above);
- exposure to tobacco smoke anywhere else indoors (same detail as above).

The questionnaire, common to all centers, was translated from English into seven languages (Cantonese Chinese, Mandarin Chinese, German, Greek, Italian, Japanese, and Polish) and tested in a preliminary version in each center. The final version of the questionnaire was again pilot-tested, as were the procedures for urine sample collection.[5]

Biochemical markers of exposure

Measurement of nicotine or its metabolite, cotinine, has been widely used to measure tobacco use and exposure to ETS.[8] Cotinine exhibits a half-life of elimination of about 18 h in active smokers and may be somewhat longer in exposed nonsmokers.[8] Its presence in urine,

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therefore, comes predominantly from exposure to tobacco during the three to four days prior to sample collection.

Spot urine samples were collected from each subject immediately after the interview. Samples were split into aliquots and frozen at − 10°C to − 20°C until shipment in dry ice to IARC and the American Health Foundation. All specimens were received in good condition and were analyzed for cotinine and creatinine.

Cotinine was quantitated by radioimmunoassay according to the method of Haley *et al.*[9] after a modification of the antibody of Langone *et al.*[10] The inter- and intra-assay coefficients of variation at 2 ng/ml were 11 and seven percent, respectively. Creatinine was determined on a Kodak Ektachem 400 Clinical Chemistry Analyzer.

Cotinine levels were adjusted for urine flow based on creatinine values. Creatinine excretion is fairly constant for individuals, although differences between sexes and over age groups do occur.[3] Additionally, smokers have been reported to excrete higher levels of creatinine than do nonsmokers.[11] Since the current study was conducted on only nonsmoking women, and all statistical analyses were standardized for age, adjustment by creatinine was considered appropriate. Adjustment was done by using cotinine/creatinine ratio or by controlling for creatinine as an independent variable in the regression analyses.

Statistical methods

For each center, the mean value of urinary cotinine as well as of duration of exposure and number of cigarettes to which the subject was exposed were adjusted for age and, when appropriate, for sampling categories of exposure. Adjustment was made by direct standardization over 12 subgroups of age (derived from the age distribution of the entire sample) and four sampling categories of equal size (25 percent each). The relation between urinary cotinine and indicators of exposure was investigated by regression analysis. The dependent variable (cotinine) was included in the model after log transformation as $\log(x + 1)$ in order to reduce the skewness of its distribution. Adjustment was made for potential confounding factors by including the variables 'center' and 'sampling categories' as covariates in the regression model. Both variables were treated as categorical on 13 and four levels, by inclusion in the model of 12 and three dummy variables, respectively. Adjustment was also made for age and urinary creatinine included as continuous variables.

Results

This paper presents the information on ETS exposure of 1,369 subjects (out of a total of 1,426) from 13 international centers who gave complete answers to the questionnaire and provided a urine sample of at least 6 ml containing physiological levels of creatinine. Most of the centers were able to recruit approximately 50 percent of women who were currently married to a smoker and 50 percent who were currently employed outside the home (Table 1). In Trieste and Toronto, however, the proportion of employed women was much lower. The mean age of women who participated in the study was 51 years, with a range among centers from 42 – 60 years.

The distribution of cotinine, following creatinine adjustment for the 1,369 women in the study is shown in Figure 1. The shape of the distribution is asymmetric even after log transformation, with a long tail to the right.

Of the total, 270 subjects (19.7 percent) had cotinine levels reported as nondetectable (below 2 ng of absolute concentration). For purposes of simplicity, this is indicated in the data as zero. The median value for the total population was 6 ng/mg, the cut-off point of the highest quintile was 14.5 ng/mg, and of the highest decile 24 ng/mg. Forty-seven subjects (3.4 percent of the total) had values above 50 ng/mg, and 26 subjects had values above 100 ng/mg (1.9 percent).

For the subsequent analyses, women who were likely to have personally used tobacco products in the past few days were identified and excluded. While there is no clear-cut value which discriminates occasional smokers from subjects heavily exposed to ETS, data distributions and analyses of several recent studies were considered in establishing this cut-off point.[12–15] In controlled high-level exposures in chambers[16] and aircraft,[17] urinary excretion of cotinine has reached a concentration of 55 ng/mg creatinine. In our data, a cut-off point of 50 ng/mg creatinine may suggest that the proportion of women misreporting their active smoking habit was 3.4 percent, whereas a much more conservative cut-off point at 100 ng/mg would result in a proportion of 1.9 percent. Based upon the studies just cited, we excluded from the analyses the 47 women whose cotinine/creatinine ratios were above 50; this left 1,322 women in the study. It should be noted that this exclusion did not materially modify the results.

Average age-adjusted cotinine/creatinine levels found in the 13 centers are shown in Figure 2. For each center two averages are provided, based either on all subjects or on those subjects for whom cotinine levels were greater than zero. The former is obviously partially determined by the sampling procedure and by the proportion of potentially nonexposed women actually included in the study in each center (Table 1). The differences by center are clearly large and statistically significant. The lowest values (for all individuals with cotinine greater than zero) were observed in Honolulu, Shanghai, and Chandigarh, while the three highest values came from Trieste, Los Angeles, and Warsaw. In Trieste and Hong Kong, all

Table 1. Percentage distribution by center of the study subjects according to whether or not the subject was married to a smoker and whether or not she was employed

Center	Percentage distribution				No. of subjects	Age (mean ± SD)
	Employed		Not employed			
	Not married to current somker	Married to current smoker	Not married to current smoker	Married to current smoker		
Bremen	29.5	13.7	34.7	22.1	95	49.3 ± 6.3
Turin	30.1	21.5	30.1	18.3	93	50.4 ± 6.9
Trieste	47.4	40.2	3.1	9.3	97	56.7 ± 14.0
Warsaw	31.5	21.4	22.1	25.2	131	44.8 ± 11.6
Athens	19.8	22.8	27.7	29.7	101	42.5 ± 7.5
Chandigarh	25.8	23.7	25.8	24.7	97	44.8 ± 6.6
Hong Kong	24.5	22.3	23.3	30.1	103	53.1 ± 9.0
Shanghai	27.3	25.2	26.3	23.2	99	56.6 ± 8.0
Sendai	25.0	19.6	29.1	26.4	148	50.3 ± 6.1
Honolulu	41.4	12.1	28.3	18.2	99	59.3 ± 7.8
Los Angeles	16.0	15.0	32.0	39.0	100	49.5 ± 11.0
New Orleans	20.8	25.5	29.2	24.5	106	50.2 ± 8.2
Toronto	51.0	19.0	25.0	5.0	100	60.2 ± 8.8
All	30.0	21.4	24.2	22.7	1369	51.4 ± 10.5

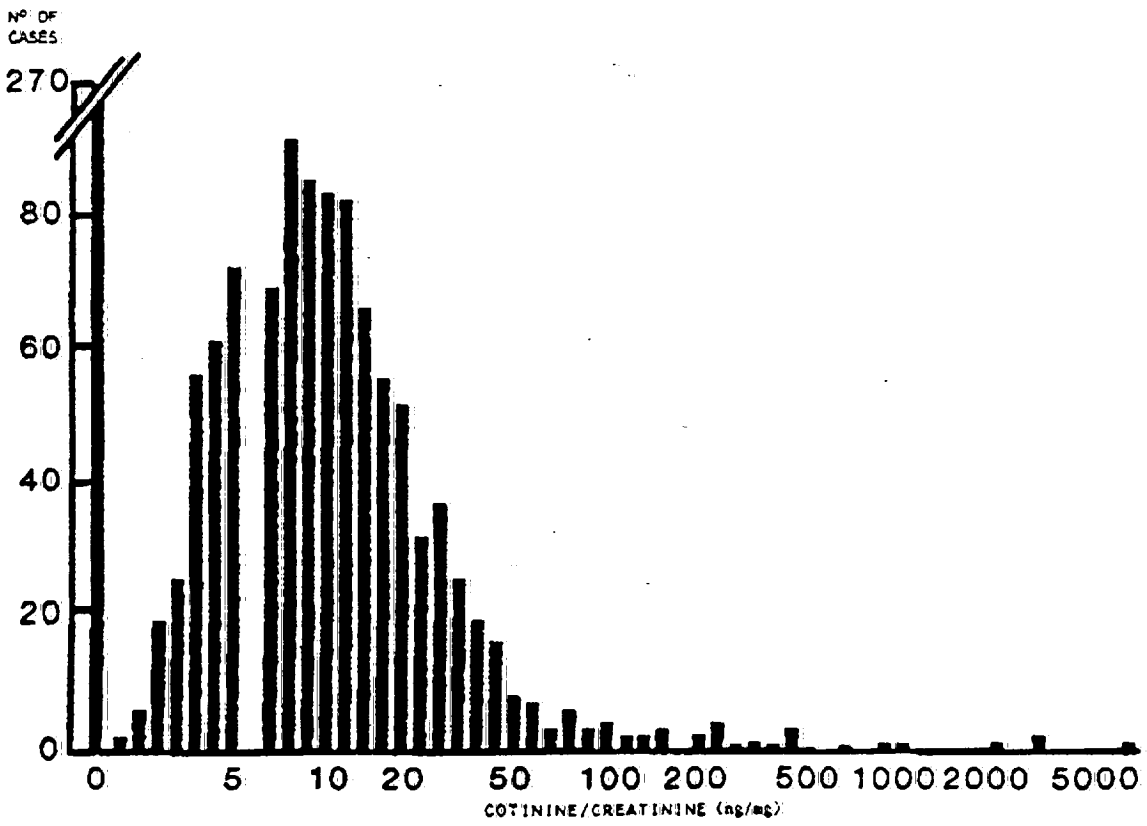


Figure 1. Distribution of 1,369 nonsmoking married women by urinary cotinine/creatinine levels on a logarithmic scale.

or almost all of the subjects had detectable levels of cotinine in their urine.

The age-standardized mean levels of cotinine/creatinine ratios for each of the four sampling categories are shown in Figure 3a. As expected, there was a gradient in average cotinine levels across presumed categories of exposure. Women whose husbands did not smoke and who were not employed had the lowest mean levels. At the other extreme was the group of women married to a smoker and employed (and thus presumed to be exposed both at home and at work) followed very closely by those married to a smoker but not employed. Women employed but not living with a smoker had levels only slightly increased compared to those neither married to a smoker nor employed.

Subjects were then reclassified according to the exposure to ETS they actually reported for the four days preceding the interview (Figure 3b). A clear linear increase in mean cotinine/creatinine levels was observed from the group of women not exposed either at home or at work up to the group of those exposed both at home and at work. Average cotinine/creatinine values were higher for women exposed to ETS from the husband but not at work than from those exposed at work but not from the husband ($P < 0.001$).

Figure 3c shows the average cotinine/creatinine levels for the two extreme groups of women who reported no exposure at all from any of the sources considered (3.03 ng/mg) and for those exposed to all sources, *i.e.* husband, work, home, public places, and vehicles (18.47 ng/mg).

Self-reported exposure on different occasions during the four days preceding the interview was summarized in four cumulative indicators: (i) the number of cigarettes to which the subject was exposed; (ii) the duration of her exposure to ETS; (iii) the ratio of the number of cigarettes divided by the volume (m^3) of indoor places where exposure occurred, as a measure of ETS concentration in the ambient air; (iv) an estimate of total dose obtained by multiplying the concentration of ETS in each place (no. of cigarettes/m^3) by the time spent in that particular place. These four indices were computed separately for the cumulative exposure to ETS from the husband and the workplace and for the cumulative exposure to all sources considered.

The relationship between self-reported exposure and

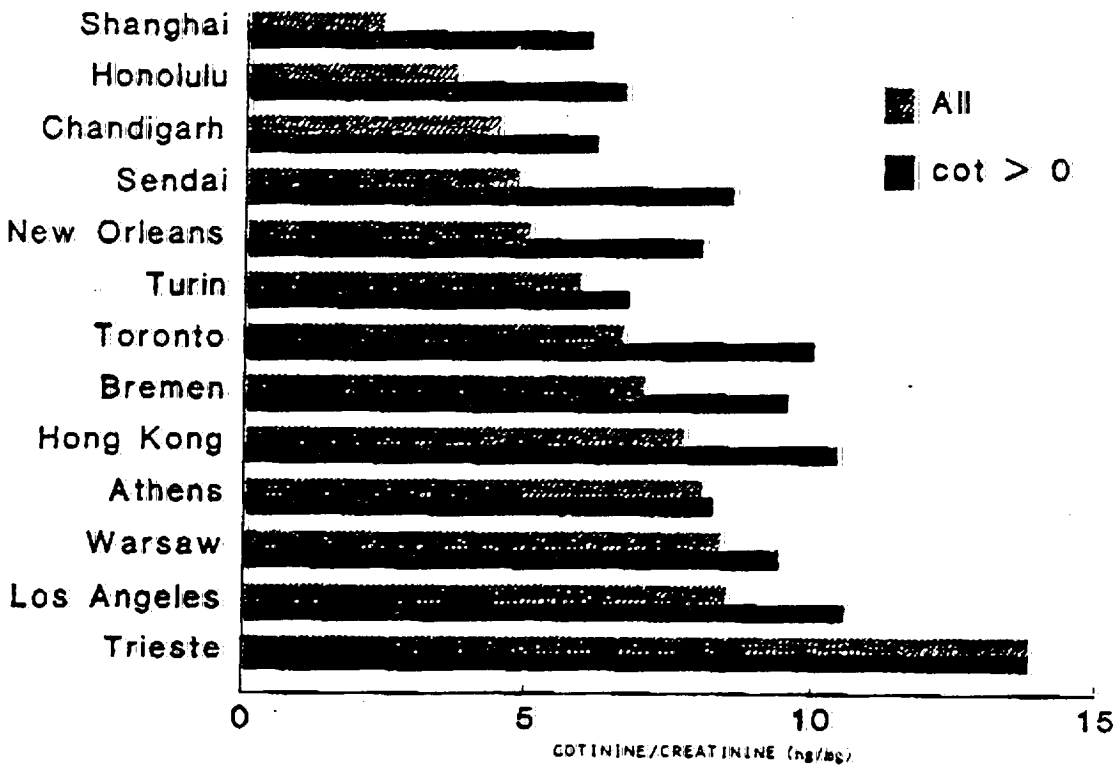
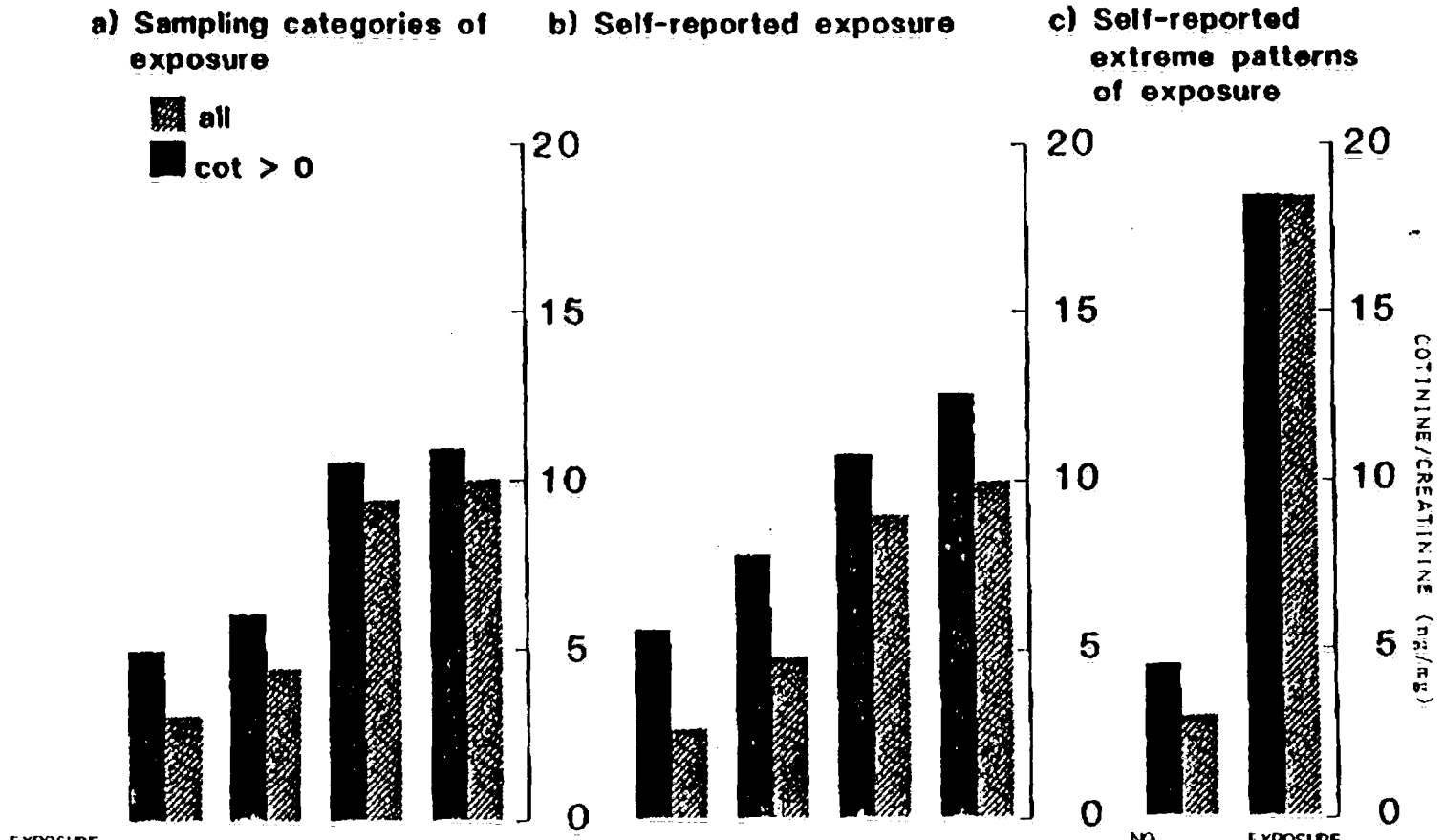


Figure 2. Average urinary levels of cotinine/creatinine levels (ng/mg) among nonsmoking women in 13 study centers.



EXPOSURE AT WORK:	–	+	–	+	–	+	–	+	NO EXPOSURE REPORTED	EXPOSURE FROM ALL SOURCES
EXPOSURE AT HOME:	–	–	+	+	–	–	+	+		
ALL N°.	405	350	274	293	629	210	359	124	334	36
MEAN	3.1	4.5	9.5	10.1	2.7	4.8	9.0	10.0	3.0	18.5
COT>0 N°.	271	268	245	269	429	172	335	117	209	36
MEAN	5.0	6.1	10.6	11.0	5.6	7.8	10.8	12.6	4.5	18.5

Figure 3. Average cotinine/creatinine levels (ng/mg) for subgroups of nonsmoking women defined either by sampling categories of exposure or by self-reporting exposure to ETS from different sources during the four days preceding collection of the urine sample

urinary cotinine levels was investigated by regression analysis after adjustment for center, age and creatinine (Tables 2 and 3). Age was dropped from the final regression model as it did not contribute significantly to predicting cotinine variations once other predictors were in the model. Two types of indicators of exposure were tested as predictors of urinary cotinine levels:

(i) simple dichotomous indicators of either positive or negative reporting of exposure to ETS from the husband, other people at home, work, public places, and vehicles;

(ii) quantitative estimates of daily exposure, such as total duration of exposure, total number of cigarettes, number of cigarettes divided by indoor air volume and ETS 'dose' (cigarettes × time/m³). These indicators were computed separately for specific sources of exposure and for all sources combined.

Table 2. Regression analyses of urinary cotinine on dichotomous indicators of exposure to ETS

Type of exposure to ETS	Beta ± SE	*P*
Husband[a]	6.22 ± 0.40	$< 10^{-5}$
Work	2.41 ± 0.49	$< 10^{-5}$
Husband & work	9.00 ± 0.76	$< 10^{-5}$
Public places, vehicles, other	3.12 ± 0.45	$< 10^{-5}$

Beta values can be interpreted as the average increase in ng of cotinine above baseline level for exposed as compared to nonexposed subjects.
[a]Model : log (cotinine + 1) = age + log creatinine + center$_2$ + ... + center$_{11}$ + sampling categories + 'husband' (0,1). The variable 'husband' was then replaced by the other variables in the table, taken one-by-one.

The results of the regression analyses on simple dichotomous indicators of exposure are shown in Table 2. Exposure to ETS from the husband during the four days preceding interview is a strong predictor of cotinine levels, highly statistically significant ($P < 0.0001$). Simply reporting exposure to ETS from the husband would predict an increase of 6.2 ng cotinine (adjusted for creatinine) above the baseline level. Indicators of exposure to ETS at work and from public places and vehicles were also significant predictors of cotinine levels, although less strong than exposure to ETS from the husband in terms of predicted increase in cotinine. Reporting of combined exposure to ETS from the husband and work resulted in a predicted average increase of 9 ng cotinine, which is highly statistically significant.

The quantitative relation between the predictors derived from the questionnaire and urinary cotinine levels was further analyzed by including, one-by-one in separate regression models, different specific and combined estimates of exposure (Table 3). Duration of exposure to ETS (in minutes) from all sources combined was a strong predictor of cotinine levels ($P < 0.0001$). Among the specific sources of exposure, the duration of daily

Table 3. Regression analyses of urinary cotinine on quantitative indicators of exposure to ETS

Quantitative exposures	Beta ± SE	*P*	Increase in daily exposure which predicts an increase of 5 ng/ml of urinary cotinine above baseline
Duration of exposure to ETS[a] (min/day) from:			
All sources combined	0.0263 ± 0.0014	$< 10^{-5}$	3 h 10 min
Husband	0.0354 ± 0.0023	$< 10^{-5}$	2 h 30 min
Work	0.0159 ± 0.0024	$< 10^{-5}$	5 h 15 min
Husband + work	0.0261 ± 0.0016	$< 10^{-5}$	3 h 11 min
Public places, vehicles, other	0.0324 ± 0.0036	$< 10^{-5}$	3 h 34 min
Number of cigarettes/day from[a]:			
All sources combined	0.0767 ± 0.0063	$< 10^{-5}$	-
Husband	0.7693 ± 0.0484	$< 10^{-5}$	6.5 cigs/day
Work	0.0600 ± 0.0088	$< 10^{-5}$	83.3 cigs/day
Public places, vehicles, other	0.0701 ± 0.0122	$< 10^{-5}$	71.3 cigs/day
ETS estimated dose (cigarettes × time/m³)			
All sources	0.0311 ± 0.0024	$< 10^{-5}$	14.0 cigs × 8 h/40 m³
Husband	0.0569 ± 0.0058	$< 10^{-5}$	7.2 cigs × 8 h/40 m³
Work	0.0253 ± 0.0029	$< 10^{-5}$	17.9 cigs × 8 h/40 m³

[a]Figures not adjusted for volume of the room

exposure to ETS from the husband was the strongest predictor. To help in the interpretation of the regression coefficient, we expressed the results according to the duration of exposure which predicts an arbitrarily defined increase of 5 ng in the cotinine level. Exposure to ETS from the husband for 2 h 30 min per day would predict a quantitatively similar increase to 5 h 30 min exposure at work, and 2 h 34 min from miscellaneous sources, which include public places, vehicles, and other people at the subject's home. From all sources combined, 3 h 10 min of exposure predict an increase of 5 ng of cotinine.

The number of cigarettes to which the subject reported being exposed was also strongly related to urinary cotinine. The exposure level which would predict the arbitrarily-chosen increase of 5 ng of cotinine was 6.5 cigarettes/day from the husband (figure compatible with experimental exposure studies) and 83.3 cigarettes/day at work.

When the number of cigarettes is corrected for duration of exposure and room volume, the values predictive of an increase of 5 ng cotinine become 7.2 cigarettes/8 h of exposure/40 m^3 from the husband, and 17.9 cigarettes/8 h/40 m^3 from work. In other words, once duration of exposure and room volume are taken into account, the regression coefficient indicates that a similar increase in cotinine is predicted when the husband smokes in the presence of the subject about half the number of cigarettes to which the subject is exposed at work. To further explore the relation of cotinine level with duration of exposure and number of cigarettes from different sources, we fitted a linear regression model in which duration of exposure and number of cigarettes from husband, work, and other sources of ETS were included simultaneously. Duration of exposure and number of cigarettes from husband, work, and other sources of ETS were included in the same regression model and statistical significance computed by step-down analysis. The results shown in Table 4 indicate that both number of cigarettes and duration of exposure from different sources retain their statistical significance after reciprocal adjustment. The results also suggest that, for exposure to ETS at work and in public places, vehicles, and other sources, cotinine level is better predicted by duration of exposure than number of cigarettes/day. For exposure to ETS from the husband, cotinine levels are better predicted by the number of cigarettes smoked daily by the husband in the presence of his spouse than by duration of exposure.

Table 4. Regression analyses on number of cigarettes per day and duration of exposure adjusted simultaneously one for the other and for the three different sources considered

	Beta ± SE
Duration of exposure	
Husband	0.0039 ± 0.0010
Work	0.0036 ± 0.000*
Public places, vehicles, other	0.0043 ± 0.003*
No. of cigs/day from	
Husband	0.1519 ± 0.020*
Work	0.0069 ± 0.002*
Public places, vehicles, other	0.0847 ± 0.0112

Discussion

The present study was designed and implemented to evaluate the self-report of ETS exposures among women married to smokers or exposed outside the home. As a multicenter study involving 13 centers from 10 countries, it had the further potential to evaluate differences in exposure across local settings and varied sources of potential exposure.

The mean cotinine levels across centers are similar to those observed in other studies[3,14,16,19] and support the hypothesis that persons who report ETS exposure have detectable cotinine levels. Approximately 20 percent of the group had cotinine levels below the reliable limits of detection of the cotinine assay (2 ng/ml). Analyses of self-report for these subjects revealed that 60 percent of them were not exposed outside the home, and 89 percent reported that they had no exposure from a husband who smoked.

To avoid possible misclassification of active smokers as nonsmokers, we excluded from the analysis all women with a cotinine level above 50 ng/mg even though, as already stated, this did not alter the results. Examination of the self-reported exposure of these subjects showed that 81 percent reported exposure to tobacco smoking by their husband while 49 percent reported heavy exposure (more than 4 h/day) outside the home. While it is possible that these women were only the recipients of heavy exposure, concordance of behavior among spouses raises the possibility of light smoking by this group.[6] This subgroup will be the subject of another report.

The mean cotinine level observed across centers, after adjustment for index, reveals varying proportions of exposed persons at each center, with the lowest levels of exposure occurring in Honolulu, Shanghai, and Chandigarh. In contrast, Trieste, Los Angeles, and Athens had significantly higher average levels of cotinine. The differences in average exposure shown in Figure 2 were somewhat attenuated once indicators of exposure (duration, concentration, etc.) were introduced in the regression model, but did not disappear. On the other hand, the relations we found between quantitative indicators of exposure and urinary cotinine were not statistically different between study centers. This was tested by

introducing in the statistical model the interaction terms between indicators of exposure and 12 dichotomous variables indicating the 13 study centers. These results suggest that women are exposed to a background level of ETS which may often remain unnoticed. The perceived exposure to the sources considered in our questionnaire is related to an increase in urinary cotinine above background level which is qualitatively and quantitively consistent across centers.

Cotinine levels in women exposed only to their husbands' smoking were higher than those in women exposed at work only. Home exposure was the greatest determinant of urinary cotinine, with the smoking habits of the husband being the strongest predictor in quantitative terms. This is consistent with data from the US which shows an effect of workplace exposure, but a greater effect for home exposure.[19]

In a recent study on adult nonsmokers conducted in New Mexico,[20] the authors found a correlation of only 0.29 between urinary cotinine and exposure to ETS during the preceding 24 h. In our study, we collected information on exposure to ETS during the day the urine sample was taken and during the preceding three days. We found that the correlation coefficients between cotinine and cumulative duration of exposure were between 0.40 and 0.51 ($P < 0.001$) for nine out of 13 centers and between 0.30 and 0.40 ($P < 0.01$) for two other centers. In only two centers were the correlation coefficients lower than 0.30.

Overall, our statistical analyses of different quantitative indices derived from self-reported history of exposure to ETS indicated that the time spent in an indoor place when somebody was smoking is a more correct predictor of cotinine levels than the number of cigarettes smoked. This may be explained in two ways. First, it is probably easier for a person to estimate the time spent somewhere where they are exposed to ETS rather than to remember the number of cigarettes smoked in their presence. Thus, the estimate of duration of exposure may be less affected by random misclassification than by the estimate of number of cigarettes. The second explanation may be that the concentration of ETS in indoor air varies as a function of specific place, time, and persons. Thus, the duration of time when the subject breathes the mixture of air and tobacco smoke becomes the main determinant of the intake of nicotine.

In conclusion, these results indicate that, when appropriately questioned, women who do not smoke can provide estimates of their exposure to ETS which are good indicators of their biochemically measured exposure levels. It also appears that in future studies of the health effects of ETS, attention should focus on daily duration of exposure and the volume of the indoor places where exposure occurred.

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